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Frontline Alectinib Upholds OS Benefit in Advanced ALK+ NSCLC

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Alectinib (Alecensa) demonstrated a 22% reduction in the risk of death compared with crizotinib (Xalkori) in the frontline setting of patients with advanced ALK-positive non–small cell lung cancer (NSCLC), which was found to be clinically meaningful, according to final results of the phase 3 ALEX trial (NCT02075840), which were presented during the European Society for Medical Oncology (ESMO) Congress 2025.1

Data showed that at a median follow-up of 53.5 months with alectinib and 23.3 months with crizotinib, the median overall survival (OS) was 81.1 months (95% CI, 62.3-not estimable) compared with 54.2 months (95% CI, 34.6-75.6), respectively (HR, 0.78; 95% CI, 0.56-1.08; stratified log-rank P = .1320). The 7-year OS rate was 48.6% with alectinib vs 38.2% with crizotinib.

“This is probably one of the longest OS [rates] we’ve ever reported for patients with stage IV non–small cell lung cancer. Despite the numerical difference, the HR was 0.78 …, so, not significant,” lead study author Tony S. K. Mok, BMSc, MD, FRCP(C), FRCP(Edin), FHKCP, FHKAM(Medicine) said in a presentation of the data, explaining that the study was not powered for OS. “Fifty percent of patients alive at 5 years in a randomized phase 3 study of stage IV lung cancer, I think this is actually an achievement.”

The long-term OS improvement with alectinib, which was beneficial but not significant, was observed across most patient subgroups, except for active smokers (HR, 1.75) and those with an ECOG performance status of 2 (HR, 1.47). In those with central nervous system (CNS) metastases, however, data showed that the largest benefit was observed in patients who had undergone radiation (HR, 0.62).

Earlier results of ALEX led to the FDA approval of alectinib in April 2024 in the frontline setting for patients with advanced ALK-positive NSCLC.2,3

In the open-label, multicenter phase 3 ALEX trial, patients with advanced ALK-positive NSCLC were randomly assigned to receive 600 mg of twice-daily alectinib or 250 mg of twice-daily crizotinib until disease progression, unacceptable toxicity, withdrawal from study, or death. No crossover was permitted before disease progression. Patients also underwent imaging every 8 weeks.

Patients must have been 18 years or older, have no prior systemic therapy, and an ECOG performance status of 0 to 2. Stratification factors included ECOG performance status (0 or 1 vs 2), race (Asian vs non-Asian), and baseline CNS metastases (yes vs no).

The primary end point was investigator-assessed progression-free survival (PFS) via RECIST v1.1 criteria, with secondary end points being independent review committee–assessed PFS, time to CNS progression, objective response rate, duration of response, OS, and safety.

Prior reported data of the final PFS analysis, which had a data cutoff date of November 30, 2018, showed an investigator-assessed median PFS of 34.8 months with alectinib vs 10.9 months with crizotinib (P <.0001).4 At a median follow-up of 48.2 months, OS data were immature, and the

median OS was not reached with alectinib vs 57.4 months with crizotinib (stratified HR, 0.67; 95% CI, 0.46-0.98).

At the ESMO Congress 2025, Mok, who serves as the Li Shu Fan Medical Foundation endowed Professor and chairman of the Department of Clinical Oncology at the Chinese University of Hong Kong, presented on the final OS analysis and long-term safety data after an additional 6 years of follow-up from the prior OS analysis. The data cutoff date was April 28, 2025.

Patient characteristics were generally well-balanced between both arms. CNS metastases via an independent review committee were present in 42.1% of alectinib-treated patients (n = 152) vs 38.4% of those on crizotinib (n = 151), and 17.1% and 13.9% of patients, respectively, received prior brain radiation.

Additional data showed that the next 1 or more lines of ALK TKI therapy in the alectinib (37.5%) and crizotinib arms (47.7%) included lorlatinib (18.4% and 11.9%, respectively), brigatinib (10.5% and 10.6%), crizotinib (9.2% and 6.6%), alectinib (8.6% and 25.2%), ceritinib (6.6% and 19.2%), ensartinib (0.7% and 0%), NVL 655 (0.7% and 0), and APG 2449 (0 and 0.7%).

Mok noted these OS results are not statistically significant, potentially due to confounded data from the crossover arm of crizotinib-treated patients to alectinib.

In exploring the OS of patients with CNS metastases at baseline, the median OS was 63.4 months in those on alectinib (n = 59) compared with 30.9 months for those on the crizotinib arm (n = 53), leading to a 32% reduction in the risk of death (HR, 0.68; 95% CI, 0.40-1.15). For those without CNS metastases on alectinib (n = 93) or crizotinib (n = 98), the median OS was 94.0 months vs 69.8 months, respectively (HR, 0.87; 95% CI, 0.58-1.32).

Furthermore, in the group of patients who received prior brain radiation, the median OS was 92.0 months with alectinib (n = 25) compared with 39.5 months in those who received crizotinib (n = 18; HR, 0.62; 95% CI, 0.24-1.60). Those who did not have prior brain radiation had a median OS of 46.9 months with alectinib (n = 34) vs 23.7 months on crizotinib (n = 35; HR, 0.73; 95% CI, 0.38-1.38).

Investigator-assessed DOR in responders was a median of 42.3 months (95% CI, 31.3-51.3) with alectinib (n = 126) vs 11.1 months with crizotinib responders (n = 11; 95% CI, 7.9-13.0), leading to an HR of 0.41 (95% CI, 0.30-0.56).

Regarding safety, the median duration of treatment was 28.1 months (range, 0-127) with alectinib and 10.8 months with crizotinib (range, 0-123). The most common adverse effects (AEs) that led to dose reductions or discontinuations with alectinib comprised increased blood bilirubin (5.3% and 3.3%, respectively). For crizotinib, this included increased alanine aminotransferase (8.6% and 6.6%). Grade 3 to 5 AEs were similar between the alectinib and crizotinib arms (57.9% vs 57.6%, respectively), and serious AEs were 46.1% vs 31.8%; treatment-related AEs were 82.2% vs 89.4%. AEs with alectinib that led to death, treatment discontinuation, dose reduction, and dose interruptions occurred in 6.6%, 17.8%, 23.0%, and 32.2%, respectively. On the crizotinib arm, these rates were 4.6%, 14.6%, 19.9%, and 28.5%, respectively.

The most common grade 3 to 5 AEs between both arms included anemia (7.2% with alectinib vs 0.7% with crizotinib), increased alanine aspartase (5.3% vs 10.6%), pneumonia (5.3% vs 2.0%), urinary tract infection (5.3% vs 0.7%), increased ALT (4.6% vs 16.6%), increased blood bilirubin (4.6% vs 0%), increased blood CPK (3.3% vs 4.6%), neutropenia (0% vs 6.0%).

Two percent of on-study deaths (n = 3) of unknown cause, with no autopsy performed, were suspected to be unrelated to alectinib.

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